Claim 44:

The method of claim 41, wherein said anti-L-selectin antibody is HuDreg 200 or HuDreg 55, wherein antibody HuDreg 55 comprises a light chain variable region having an amino acid sequence as set forth in SEQ ID NO:2 and a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO:4, and antibody HuDreg200 comprises a light chain variable region having an amino acid sequence as set forth in SEQ ID NO:5 and a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO:6.

Claim 45:

The method of claim 41, further comprising administering 1-3 doses of anti-L-selectin antibody to said patient, each of said doses containing 1-4 mg/kg of body weight of said patient.

REMARKS

Entry of the amendment is requested. Claims 22 - 45 will be pending. No fee is due in connection with these claims.

Applicants will address each point raised by the examiner.

Point 1 is confusing. The examiner states that claims 1, 2, 5-11, 13-24, 27, and 28 read on the elected species (anti-L-selectin antibodies), but claims 3, 4, 12, 25 and 26 do not. Claims 3, 12 and 26 read on anti-E-selectin and have been withdrawn by the examiner; claim 4 reads on anti-P-selectin, and has been withdrawn as has claim 26; however, claim 23 also reads on anti-P-selectin and has been deemed to read on the elected species. Please clarify.

With respect to point 2, in order to facilitate issues, applicants have added the language of claims 22-28 to the specification so as to provide written description for the claims. The examiner has not set forth a lack of enablement rejection of these claims.

Point 3 requires no comment.

With respect to point 4, 37 CFR § 1.84 need not be complied with until allowance.

With respect to points 5 and 6, applicants have reviewed the specification and do not find spelling errors, trademarks, or nucleotide/amino acid sequences in the specification. The examiner has not pointed out where these arise in the specification and is asked to do so.

Point 6 has been addressed, supra.

Turning to point 7A, sequence information is not recited in the claims.

Claim 22 is amended to refer to prevention of multiorgan failure, thereby rendering the issues raised in 7B moot.

Points 8 and 9 set forth sections of 35 USC § 102 and § 103.

Points 10, 11, and 12 set forth anticipation rejections, of claims 1, 2, 5-11, 13-24, 27 and 28 (all examined claims) in view of Co, WO94/12215, or Lefer, WO95/95181, and claims 1, 2, 6, 10, 11, 20, 22, 23 and 28 in view of U.S. Patent No. 5,679, 346 to Tedder. Applicants traverse.

With respect to both Co and Lefer, the examiner states:

> "Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention."

This is not the standard set forth in 35 USC § 102, or in Federal Circuit precedent interpreting the statute. The standard which must be met is that all features of what is claimed must be taught explicitly. The examiner, should he continue to rely on the standard set forth in the action and quoted supra, is called upon to provide a precise citation to statute or case law, expressly setting forth this standard. Applicants are not requesting an interpretation of case law. The have requested a citation providing the language.

The examiner goes on to state

> "The claimed functional limitations addressed by the applicant would be inherent properties of the referenced method with L-selectin specific antibodies."

The import of this statement is not understood. It is agreed that products have inherent properties; however, applicants are not claiming products. They are claiming methods. A first method is not inherent in a second method. Rather, for anticipation to lie, the method itself must be taught. Such is not the case with the prior art.

The Co reference cites a number of possible approaches one could take with selectin specific antibodies. There is no mention of polytrauma therein, nor is there any teaching which would suggest this. (Please see example 1, paragraph 1, for a discussion of severe polytrauma.) Applicants explain, at great length in the application, that the pathology of severe polytrauma involves

leukocytes, mediator systems and other factors some of which are listed at page 2 of the application. It is incorrect to think of the claimed invention as an aspect of the treatment of ischemic-profusion injury, which is what Co addresses. One cannot draw any conclusions as to extrapolating Co's work, as the art has noted failure in this regard. See, e.g., "LeukArrest fails in haemorrhagic shock," a copy of which is attached hereto.

The evidence actually suggests that in the treatment of severe polytrauma, especially multiple organ failure associated therewith, that treatment with L-selectin specific antibodies is not recommended. They did not exhibit any effect with simple trauma or hemorrhagic shock, which would suggest that in more complex pathologies they would show no effect either. Hence, Co cannot be said to teach or suggest what is claimed. One finds no mention in Co, for example, of heart/lung machines, or any of the conditions elaborated in the claims.

Such is also the case with Leifer and Tedder. The examiner has made the same argument vis-à-vis these references as was made for Co. The do not teach anything more than Co does, and hence do not support the rejections as set out in points 11 and 12 of the office action.

The rejection at point 13, made under 35 USC § 103, adds 5 additional references to the three references discussed supra; however, none of these references remediate the failings of the primary references, which are discussed supra. In view of these failings, the rejection under 35 USC § 103 cannot be maintained.

Reconsideration of the rejection, and allowance of claims 22, 23, 27, and 29-45 is believed proper and is urged.

Respectfully submitted,

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Janssen withdraws Hismanal worldwide

Janssen has voluntarily withdrawn its antihistamine product, Hismanal (astemizole), worldwide.

The move follows a series of labelling changes and warnings of adverse effects due to interactions of the product with other medications. The drug had also been switched from OTC to prescription-only status in many markets, and sales had fallen sharply.

Janssen said the discontinuation of Hismanal was a commercial decision driven by its falling market share. The company declined to give sales figures for the product, but said it took only a "very small" share of the antihistamine market. In 1998, Hismanal was reported to account for about 3% of the $1.5 billion US non-sedating antihistamine market, but this will have declined further since then with the stronger side-effect warnings.

The US FDA said it supported Janssen's decision to withdraw Hismanal, given its risk/benefit profile and the large choice of other antihistamines now available.

Hismanal was launched in 1988, and became one of Janssen's best selling products, being one of the first non-sedating antihistamines along with Merrell Dow's terfenadine. However, Hismanal sales started to decline in the early 1990s with the introduction of many other non-sedating antihistamines.

Sales fell more quickly after reports of potentially serious interactions with other drugs and warnings of cardiovascular events with high doses. Its major problem was that the enzymes that metabolised Hismanal were blocked by many other medications, including several commonly used antibiotics and antidepressants, leading to increased plasma levels of astemizole and an increased risk of QT prolongation. It was also contraindicated in patients with liver disorders and was not to be taken with grapefruit juice.

The Hismanal situation resembles closely that of its major competitor, terfenadine, which was withdrawn from the US market by Hoechst Marion Roussel in 1998 because of similar interactions, after it launched the safer metabolite, fexofenadine (Allegra).

This seemed to be a strategy that Janssen was also going to follow, as J&J (Janssen's parent company) had a deal with Sepracor for the joint development of a safer astemizole metabolite, norastemizole. However, last month J&J pulled out of this agreement, citing the high cost of establishing a new brand in the very competitive OTC antihistamine market, and the lack of synergy with other J&J products (*Scrip* No 2439, p 11).

The major player in the non-sedating antihistamine market is now Schering-Plough's Claritin (loratadine), which has sales of more than $2 billion, followed by Pfizer's Zyrtec (cetirizine), with sales of around $400 million.

Meetings

The following short courses are to be held in July in San Mateo, US: ***cGMP and Quality Issues for Biopharmaceuticals*** on the 19th-20th; ***Assay Development and Validation for Biopharmaceuticals*** on the 21st-22nd, and ***The Mechanics of Preparing INDs and NDAs for FDA Regulations*** on the 28th-30th. For details contact The Center for Professional Advancement, PO Box 1052, East Brunswick, NJ 08816, US. Tel: +1 732 613 4500. Fax: +1 732 238 9113.

LeukArrest fails in haemorrhagic shock

ICOS's humanised monoclonal leucointegrin antibody, LeukArrest (formerly known as Hu23F2G), has failed in a Phase II trial for the treatment of trauma-induced haemorrhagic shock originating from blunt or penetrating injury.

The product failed to reach its primary endpoints, a reduction in fluid replacement administered to patients in the first 24 hours after hospital admission and a reduction in the extent of multiple organ failure, or its secondary endpoints, a reduction in 28-day mortality, the number of intensive care unit-free days and the number of mechanical ventilation-free days.

Although the product did not significantly reduce the incidence of multiple organ failure, it significantly improved patients' heart and lung function. Also, the study indicated that the 75mg dose of the product inhibited the incidence of acute respiratory distress syndrome (ARDS) as measured in the first 14 days. ICOS is developing a clinical trial protocol to better understand the effect of LeukArrest on ARDS in these patients, which it says may investigate whether the product reduces the incidence of ARDS and/or death compared with placebo.

LeukArrest prevents inflammation by binding to CD11/CD18 molecules on the surface of circulating white blood cells, and stopping them attaching to the blood vessel wall. This prevents white blood cells passing from the bloodstream into tissue, an action which plays a role in inflammation. There are few potential therapies in development for the treatment of haemorrhagic shock, ICOS notes.

The trial, which was presented at the 21st annual conference on shock and the fourth International Shock Congress, involved 150 patients who were randomised to receive 25 or 75mg of LeukArrest or placebo.

LeukArrest is in a number of ongoing trials including a Phase III trial in ischaemic stroke and Phase II trials in myocardial infarction, which have completed enrolment, and in multiple sclerosis, with results expected in July. These are not affected by the latest results, says ICOS.

The company has four other products in clinical trials: the platelet-activating factor acetylhydrolase, Pafase (formerly known as rPAF-AH), which is in three Phase II trials for ARDS, asthma and post-ERCP pancreatitis; the anti-ICAM-3 antibody, ICM3, for severe psoriasis (Phase I/II); and IC14 for severe sepsis (Phase I). ICOS has formed a partnership with Lilly to develop ICOS's phosphodiesterase type V inhibitor, IC351, for the treatment of male erectile dysfunction and female sexual dysfunction (*Scrip* No 2376, p 8). It is in Phase II trials for erectile dysfunction, with launch planned for late 2001.

. . . product news in brief

■ ***Itraconazole for nail infections in Japan:*** Janssen-Kyowa has received approval from Japan's Ministry of Health and Welfare to market the oral antifungal, Itrizole (itraconazole), in the additional indication of nail infections, including those caused by candidiasis. The product was first launched on the local market in 1993, and will have the same reimbursement price, ¥715.80 ($6) per 50mg capsule, for the new indication. Novartis launched oral and topical formulations of Lamisil (terbinafine) for nail infections in Japan in 1997.